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| U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE | | ATTY DOCKET NO.: 221.P1 | SERIAL NO.: 08/900,746 |
| INFORMATION DISCLOSURE STATEMENT BY APPLICANT | | APPLICANT: Arimilli et al. | |
| (37 CFR 1.98(b)) | | FILING DATE: 7/25/97 | GROUP ART UNIT: 1613 |

U.S. PATENT DOCUMENTS

| EXAMR'S INITIALS | PATENT NO. | ISSUE DATE | PATENTEE | CLASS/ SUBCLASS | FILING DATE |
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FOREIGN PATENT DOCUMENTS

| EXAMR'S INITIALS | PATENT NO. | PUBLICATION DATE | COUNTRY | CLASS/ SUBCLASS | TRANSLATION YES/NO |
|------------------|------------|------------------|---------|-----------------|--------------------|
| | | | | | |

OTHER DOCUMENTS

| EXAMR'S INITIALS | ARTICLE |
|------------------|--|
| molc | Arimilli et al., "Synthesis, in vitro biological evaluation and oral bioavailability of 9-[2-(phosphonomethoxy)propyl]adenine (PMPA) prodrugs", 8(6):557-567, ANTIVIRAL CHEM & CHEMO, 1997 |
| molc | Arimilli et al., "Orally Bioavailable Acyclic Nucleoside Phosphonate Prodrugs: Adefovir Dipivoxil and Bis(POC)PMPA", Vol. 3 (accepted for publication), ADV ANTIVIRAL DRUG DESIGN, 1998 |
| molc | Shaw et al., "Metabolism and Pharmacokinetics of Novel Oral Prodrugs of 9-((R)-2-(phosphonomethoxy)propyl)adenine (PMPA) in Dogs", 14(12):1824-1829, PHARM RES, 1997 |

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|---|--------------------|-----------------|---------|
| EXAMINER | Michael G. Ambrose | DATE CONSIDERED | 4/13/98 |
| EXAMINER: Initial citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. | | | |

FORM PTO-1449

**U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE**
**INFORMATION DISCLOSURE STATEMENT
BY APPLICANT**

(37 CFR 1.88(d))

ATTY DOCKET NO.: 221.P1

SERIAL NO.: 08/900,746

APPLICANT: Arimilli et al.

FILING DATE: 7/25/97

GROUP ART UNIT: 1205
1613**U.S. PATENT DOCUMENTS**

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|---------------------|------------|------------------|---------|--------------------|-----------------------|
| | | | | | |

OTHER DOCUMENTS

| EXAMINER'S INITIALS | ARTICLE | |
|---------------------|---|----|
| mgd | Ikeda et al., "Studies on Prodrugs. III. A Convenient and Practical Preparation of Ampicillin Prodrugs", 32:4316-4322, CHEM PHARM BULL, 1984 | ✓ |
| mgd | Jones et al., "Minireview: nucleotide prodrugs", 27:1-17, ANTIVIRAL RES, 1995 | ✓ |
| mgd | Krise et al., "Prodrugs of phosphates, phosphonates, and phosphinates", 19:287-310, Advanced Drug Delivery Reviews, 22-May-1996 | ✓ |
| mgd | Landgrebe, John A., "Crystallization and Filtration", 3rd edition, pp. 65-77, Theory and Practice in the Organic Laboratory, 1982 | ✓ |
| mgd | Starett et al., "Synthesis, Oral Bioavailability Determination, and in Vitro Evaluation of Prodrugs of the Antiviral Agent 9-[2-(Phosphonomethoxy)ethyl]adenine (PMEA)", 37:1857-1864, J MED CHEM, 1994 | 3✓ |
| mgd | Tsai et al., "Effects of (R)-9-(2-Phosphonylmethoxypropyl)adenine Monotherapy on Chronic SIV Infection in Macaques", 13(8):707-712, AIDS RES & HUM RETRO, 1997 | ✓ |
| mgd | Tsai et al., "Prevention of SIV Infection in Macaques by (R)-9-(2-Phosphonylmethoxypropyl)adenine", 270:1197-1199, SCIENCE, 17-Nov-1995 | ✓ |

| | | |
|---|--------------------|-----------------|
| EXAMINER | Michael G. Ambrose | DATE CONSIDERED |
| 4/11/98 | | |
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U.S. PATENT DOCUMENTS

| EXAMR'S INITIALS | PATENT NO. | ISSUE DATE | PATENTEE | CLASS/ SUBCLASS | FILING DATE |
|------------------|------------|------------|----------------------|-----------------|-------------|
| <i>mofcl</i> | 3,524,846 | 8/18/70 | Moffatt et al. | — | 6/2/67 |
| <i>mofcl</i> | 4,476,248 | 10/9/84 | Gordon et al. | — | 7/25/83 |
| <i>mofcl</i> | 4,816,570 | 3/28/89 | Farquhar | 536/27 | |
| <i>mofcl</i> | 4,968,788 | 11/6/90 | Farquhar | 536/27 | 1/23/89 |
| <i>mofcl</i> | 5,142,051 | 8/25/92 | Holy et al | 544/244 | 7/17/87 |
| <i>mofcl</i> | 5,177,064 | 1/5/93 | Bodor | — | 7/13/90 |
| <i>mofcl</i> | 5,208,221 | 5/4/93 | Kim et al | 514/81 | 11/29/90 |
| <i>mofcl</i> | 5,386,030 | 1/31/95 | Kim et al | 544/243 | 2/11/93 |
| <i>mofcl</i> | 5,506,347 | 4/9/96 | Erion et al | — | 2/3/94 |
| <i>mofcl</i> | 5,512,596 | 4/30/96 | Kim et al. | 514/568 | 9/2/94 |
| <i>mofcl</i> | 5,514,798 | 5/7/96 | Bischofberger et al. | — | 2/13/95 |
| <i>mofcl</i> | 5,618,964 | 4/8/97 | Cheng et al. | — | 6/7/95 |

FOREIGN PATENT DOCUMENTS

| EXAMR'S INITIALS | PATENT NO. | PUBLICATION DATE | COUNTRY | CLASS/ SUBCLASS | TRANSLATION YES/NO |
|------------------|-----------------|------------------|---------|-----------------|--------------------|
| <i>mofcl</i> | 0 269 947 A1 | 6/8/88 | EUROPE | — | |
| <i>mofcl</i> | 0 369 409 A1 | 5/23/90 | EUROPE | — | |
| <i>mofcl</i> | 0 481 214 A1 | 4/22/92 | EUROPE | — | |
| <i>mofcl</i> | 0 632 048 A1 | 6/23/94 | EUROPE | — | |
| <i>mofcl</i> | DE 41 38 584 | 5/27/93 | GERMANY | — | |
| <i>mofcl</i> | EP 0 647 649 A1 | 4/12/95 | EUROPE | — | |
| <i>mofcl</i> | WO 88/05438 | 7/28/88 | PCT | — | |
| <i>mofcl</i> | WO 91/19721 | 12/26/91 | PCT | — | |
| <i>mofcl</i> | WO 92/01698 | 2/6/92 | PCT | — | |
| <i>mofcl</i> | WO 92/09611 | 6/11/92 | PCT | — | |

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|---|--------------------|-----------------|---------------|
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|------------------|-------------|------------------|---------|-----------------|--------------------|
| <i>mycl</i> | WO 92/13869 | 8/20/92 | PCT | — | |
| <i>mycl</i> | WO 94/03466 | 2/17/94 | PCT | — | |
| <i>mycl</i> | WO 94/03467 | 2/17/94 | PCT | — | |
| <i>mycl</i> | WO 95/07919 | 3/23/95 | PCT | — | |
| <i>mycl</i> | WO 95/07920 | 3/23/95 | PCT | — | |
| <i>mycl</i> | WO 96/18605 | 6/20/96 | PCT | — | |

OTHER DOCUMENTS

| EXAMR'S INITIALS | ARTICLE | |
|------------------|---|---|
| <i>mycl</i> | Alexander et al., "Investigation of (Oxodioxolenyl)methyl Carbamates as Nonchiral Bioreversible Prodrug Moieties for Chiral Amines", 39:480-486, J MED CHEM, 1996 | ✓ |
| <i>mycl</i> | Benzaria et al., "New Prodrugs of 9-(2-Phosphonomethoxyethyl) Adenine [PMEA]: Synthesis and Stability Studies", 14(3-5):563-565, NUCLS & NUCLT, 1995 | ✓ |
| <i>mycl</i> | Cannon, Joseph G. (Reviewer), "The Chemistry of the Carbonyl Group", Vol. II, Edited by Saul Patai, Book Review, Sep-1966 | ? |
| <i>mycl</i> | Davidson et al, "N-(Acyloxyalkyl)pyridinium Salts as Soluble Prodrugs of a Potent Platelet Activating Factor Antagonist", 37(26):4423-4429, J MED CHEM, 23-Dec-1994 | ✓ |
| <i>mycl</i> | Engel, R., "Phosphonates as Analogues of Natural Phosphates", 77(3):349-367, CHEM REV, 1977 | ✓ |
| <i>mycl</i> | Farquhar et al, "Biologically Reversible Phosphate-Protective Groups", 72:324-325, J PHARM SCI, 1983 | ✓ |
| <i>mycl</i> | Flaherty et al., "Synthesis and Selective Monoamine Oxidase B-Inhibiting Properties of 1-Methyl-1,2,3,6-tetrahydropyrid-4-yl Carbamate Derivatives: Potential Prodrugs of (R)- and (S)-Nordeprenyl", 39:4759-4761, J MED CHEM, 1996 | ✓ |
| <i>mycl</i> | Folkmann et al., "Acyloxyethyl Carbonochloridates. New Intermediates in Prodrug Synthesis", pp. 1159-1166, SYNTHESIS, Dec-1990 | ✓ |
| <i>mycl</i> | Hammer et al., "Ether, Carbonate and Urethane Deoxynucleoside Derivatives as Prodrugs", 50:609-622, Acta Chemica Scandinavia, 1996 | ✓ |
| <i>mycl</i> | Ikeda et al., "Studies on Prodrugs. III. A Convenient and Practical Preparation of Ampicillin Prodrugs", 32:4316-4322, CHEM PHARM BULL, 1984 | ? |
| <i>mycl</i> | Iyer et al., "Synthesis of Acyloxyalkyl Acylphosphonates as Potential Prodrugs of the Antiviral, Trisodium Phosphonoformate (Foscarnet Sodium)", 30(51):7141-7144, TET LETT, 1989 | ✓ |
| <i>mycl</i> | Lindahl et al., "Synthesis of an Acyloxyethyl Prodrug of the Inositol Phosphate Alpha-Trinisol", 15(5):549-554, J CARBOHYDRATE CHEMISTRY, 1996 | ✓ |

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|---|---------------------------|-----------------|
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| | FILING DATE: 7/25/97 | GROUP ART UNIT: 1413 |

| EXAMR'S INITIALS | ARTICLE | |
|------------------|---|---|
| <i>mscl</i> | Maillard et al., "Adenosine Receptor Prodrugs: Synthesis and Biological Activity of Derivatives of Potent, A1-Selective Agonists", 83(1):46-53, J PHARM SCI, Jan-1994 | ✓ |
| <i>mscl</i> | Myerson, Allan S. (editor), "Solutions and Solution Properties", p. 1 - 165, Handbook of Industrial Crystallization, 1993 | ✓ |
| <i>mscl</i> | Naesens et al., "Antiretroviral Activity and Pharmacokinetics in Mice of Oral Bis(Pivaloyloxymethyl)-9-(2-Phosphonylmethoxyethyl)Adenine, the Bis(Pivaloyloxymethyl) Ester Prodrug of 9-(2-Phosphonylmethoxyethyl)Adenine", 40(1):22-28, ANTIMICRO AG & CHEMO, Jan-1996 | ✓ |
| <i>mscl</i> | Robinson et al, "Discovery of the Hemifumarate and (alpha-L-Alanyloxy)methyl Ether as Prodrugs of an Antirheumatic Oxindole: Prodrugs for the Enolic OH Group", 39:10-18, J MED CHEM, 1996 | ✓ |
| <i>mscl</i> | Safadi et al, "Phosphoryloxymethyl Carbamates and Carbonates--Novel Water-Soluble Prodrugs for Amines and Hindered Alcohols", 10(9):1350-1355, PHARM RES, 1993 | ✓ |
| <i>mscl</i> | Sakamoto et al, "Studies on Prodrugs. II. Preparation and Characterization of (5-Substituted 2-Oxo-1,3-dioxolen-4-yl)methyl Esters of Ampicillin", 32(6):2241-2248, CHEM PHARM BULL, 19-Aug-1983 | ✓ |
| <i>mscl</i> | Samara et al., "Pharmacokinetic Analysis of Diethylcarbonate Prodrugs of Ibuprofen and Naproxen", 16:201-210, Biopharmaceutics & Drug Disposition, 1995 | ✓ |
| <i>mscl</i> | Srinivas et al., "Metabolism and In Vitro Antiretroviral Activities of Bis(Pivaloyloxymethyl) Prodrugs of Acyclic Nucleoside Phosphonates", 37(10):2247-2250, ANTIMICRO AG & CHEMO, Oct-1993 | ✓ |
| <i>mscl</i> | Srivastva et al, "Bioreversible Phosphate Protective Groups: Synthesis and Stability of Model Acyloxymethyl Phosphates", 12:118-129, BIOORG CHEM, 1984 | ✓ |
| <i>mscl</i> | Starrett et al, "Synthesis and in vitro evaluation of a phosphonate prodrug: bis(pivaloyloxymethyl) 9-(2-phosphonylmethoxyethyl)adenine", 19:267-273, ANTIVIRAL RES, 1992 | ✓ |
| <i>mscl</i> | Sueoka et al., "Pharmacokinetics of Alkoxy carbonyloxy Ester Prodrugs of PMPA in Dogs", Abstract, American Association of Pharmaceutical Science, Western Regional Meeting, April 24-25, 1997, ? | ? |
| <i>mscl</i> | Sueoka et al., "Pharmacokinetics of Alkoxy carbonyloxy Ester Prodrugs of PMPA in Dogs", Poster, American Association of Pharmaceutical Science, Western Regional Meeting, April 24-25, 1997, ? | ? |
| <i>mscl</i> | Weller et al., "Orally Active Fibrinogen Receptor Antagonists. 2. Amidoximes a Prodrugs of Amidines", 39:3139-3147, J MED CHEM, 20-Dec-1995 | ✓ |

| | | |
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